

First-Trimester Serum Kisspeptin-10 Levels as a Predictor of Spontaneous Abortion: A Prospective Cohort Study

Bilal Efe, Emin Üstünyurt, Tayfur Çift, Muzaffer Temur, Engin Korkmazer

Department of Obstetrics and Gynecology, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Türkiye

ORCID of the author(s)

BE: <https://orcid.org/0009-0006-0944-0768>
EÜ: <https://orcid.org/0000-0001-5602-6785>
TÇ: <https://orcid.org/0000-0003-4025-9343>
MT: <https://orcid.org/0000-0001-9388-3882>
EK: <https://orcid.org/0000-0001-8318-2329>

Corresponding Author

Bilal Efe

Department of Obstetrics and Gynecology, Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Türkiye
E-mail: drbilalefe@gmail.com

Ethical Approval

The study was approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital, Health Sciences University (Approval No. 2011-KAEK-25 2016/12-01; June 22, 2016).

Informed Consent

Written informed consent was obtained from the participants after they were informed about the study.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

The authors declared that this study received no financial support.

CRedit Author Statement

Bilal Efe: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft.
Emin Üstünyurt: Supervision, Writing – Review & Editing, Tayfur Çift: Supervision, Investigation, Writing – Review & Editing, Muzaffer Temur: Supervision, Investigation, Writing – Review & Editing, Engin Korkmazer: Supervision, Investigation, Writing – Review & Editing.

Use of AI Statement

No generative AI or AI-assisted tools were used in the preparation of the manuscript.

Data Availability

The data are not publicly available because they contain clinical information obtained from human participants and are subject to ethical and institutional restrictions. De-identified data may be available from the corresponding author upon reasonable request, subject to institutional and ethical requirements.

Published

2026 October 8

Copyright 2026 © The Author(s)



This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0).
<https://creativecommons.org/licenses/by-nc-nd/4.0/>



Abstract

Background/Aim: Spontaneous abortion remains a common complication of early pregnancy, and biomarkers reflecting placental function may improve risk assessment after fetal cardiac activity has been confirmed. This study aimed to evaluate the predictive value of first-trimester serum kisspeptin-10 levels for spontaneous abortion in pregnancies with confirmed fetal cardiac activity.

Methods: This prospective observational study included singleton pregnancies between 7 and 12 weeks of gestation with documented fetal cardiac activity. Serum kisspeptin-10 concentrations were measured using an enzyme-linked immunosorbent assay. Pregnancies resulting in spontaneous abortion before 20 weeks were compared with randomly selected controls whose pregnancies progressed beyond 20 weeks. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of spontaneous abortion.

Results: Among 463 eligible pregnancies, 30 resulted in spontaneous abortion, and 60 controls were selected from pregnancies progressing beyond 20 weeks. Mean serum kisspeptin-10 levels were significantly lower in the spontaneous abortion group than in controls (0.73 (0.67) ng/mL vs. 1.92 (2.78) ng/mL, $P = 0.001$). Multivariate analysis demonstrated that lower serum kisspeptin-10 levels ($P = 0.030$) and higher body mass index ($P = 0.004$) were independently associated with spontaneous abortion.

Conclusion: Lower first-trimester serum kisspeptin-10 levels are associated with an increased risk of spontaneous abortion in pregnancies with confirmed fetal cardiac activity. Kisspeptin-10 may serve as a supplementary biomarker for early pregnancy risk stratification.

Keywords: spontaneous abortion, kisspeptin-10, early pregnancy, biomarker

Introduction

Spontaneous abortion is the most common complication of early pregnancy and affects approximately 10–15% of clinically recognized gestations. Despite improvements in antenatal care and diagnostic modalities, most pregnancy losses occur during the first trimester, often without an identifiable cause [1, 2]. Importantly, even in pregnancies with confirmed fetal cardiac activity, the risk of subsequent pregnancy loss remains clinically significant and poses challenges in patient counseling and management [2, 3].

Current strategies for predicting early pregnancy loss rely primarily on ultrasonographic findings and biochemical markers such as serum β -human chorionic gonadotropin (β -hCG) and progesterone levels. However, once fetal viability has been established, the predictive performance of these markers is limited because they primarily reflect embryonic development rather than placental function [4]. Consequently, there is increasing interest in identifying biomarkers that reflect early placentation and trophoblastic activity, which play a central role in pregnancy maintenance.

Kisspeptins are a family of peptides encoded by the KISS1 gene and are well recognized for their role in regulating the hypothalamic-pituitary-gonadal axis [5-7]. Beyond their central effects, kisspeptins are highly expressed in the placenta, particularly in trophoblastic tissue during pregnancy [8]. Placental trophoblasts represent the primary source of circulating kisspeptins in pregnant women, with serum concentrations rising progressively throughout gestation and declining rapidly following delivery [8, 9].

Experimental data indicate that kisspeptins regulate trophoblast invasion, angiogenesis, and implantation through autocrine and paracrine mechanisms [10, 11]. By limiting excessive trophoblastic invasion, kisspeptins contribute to controlled placental development and stability of the maternal-fetal interface. Dysregulation of these processes has been implicated in adverse pregnancy outcomes, including spontaneous abortion, preeclampsia, and fetal growth restriction [8].

Clinical studies evaluating circulating kisspeptin levels in early pregnancy have suggested an association between reduced kisspeptin concentrations and adverse pregnancy outcomes. Lower plasma or serum kisspeptin levels have been reported in women presenting with threatened miscarriage and in those who subsequently experienced early pregnancy loss [12, 13]. However, existing studies are heterogeneous with respect to study design, gestational age at sampling, and inclusion criteria. Importantly, many studies have included pregnancies without confirmed fetal cardiac activity, limiting their applicability to clinically viable pregnancies.

Therefore, the predictive value of serum kisspeptin-10 levels in pregnancies with documented fetal cardiac activity remains insufficiently defined. The present study aimed to evaluate whether first-trimester serum kisspeptin-10 levels are associated with spontaneous abortion in singleton pregnancies between 7 and 12 weeks of gestation with confirmed fetal cardiac activity and to assess the independent predictive value of kisspeptin-10 alongside established clinical factors.

Materials and methods

Study Design and Population

This prospective observational cohort study with a nested case-control analysis was conducted at the Department of Obstetrics and Gynecology, Bursa Yüksek İhtisas Training and Research Hospital, between June 2016 and September 2016. The study was approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital, Health Sciences University (Approval No. 2011-KAEK-25 2016/12-01; June 22, 2016). The study was conducted and reported in accordance with the STROBE guidelines.

Singleton pregnancies between 7 and 12 weeks of gestation with documented fetal cardiac activity on ultrasonography were eligible for inclusion.

Exclusion criteria included multiple pregnancy, known fetal chromosomal or structural abnormalities at enrollment, ectopic or molar pregnancy, chronic systemic disease requiring medical treatment, and use of hormonal medication during early pregnancy.

Study Groups

A total of 463 eligible pregnant women were enrolled. Pregnancies resulting in spontaneous abortion before 20 weeks of gestation constituted the study group. A control group was randomly selected from pregnancies that progressed beyond 20 weeks without complications. The final analysis included 30 pregnancies in the spontaneous abortion group and 60 pregnancies in the control group.

Data Collection

Maternal age, obstetric history, body mass index (BMI), gestational age at blood sampling, and pregnancy outcomes were recorded prospectively. All participants underwent standardized ultrasonographic evaluation confirming fetal cardiac activity at enrollment.

Measurement of Serum Kisspeptin-10

Venous blood samples were obtained at enrollment. Serum samples were separated and stored in accordance with the manufacturer's instructions. Serum kisspeptin-10 concentrations were measured using a commercial human kisspeptin-10 enzyme-linked immunosorbent assay kit. Measurements were performed using a microplate washer and reader system, and results were expressed in ng/mL.

Statistical Analysis

Statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean (standard deviation) or median (range), as appropriate, and categorical variables as frequencies and percentages. Normality was assessed before selection of the statistical test. Normally distributed continuous variables were compared using Student's *t*-test, whereas non-normally distributed variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the chi-square test. Univariate logistic regression analysis was used to identify potential predictors of spontaneous abortion. Variables with $P < 0.10$ in univariate analysis were included in multivariate logistic regression models. $P < 0.05$ was considered statistically significant.

Results

Of the 463 enrolled pregnancies, 30 resulted in spontaneous abortion before 20 weeks and were included in the study group, while 60 ongoing pregnancies served as controls.

Baseline demographic and clinical characteristics are presented in Table 1. There were no significant differences between the groups in maternal age, gestational age at sampling, gravidity, parity, or smoking status ($P = 0.480$, $P = 0.620$, $P = 0.710$, $P = 0.830$, and $P = 0.690$, respectively). However, body mass index was significantly higher in the spontaneous abortion group ($P = 0.004$).

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population

Variable	Spontaneous Abortion (n = 30)	Control Group (n = 60)	P-value
Maternal age (years)	28.6 (5.1)	27.9 (4.8)	0.480
Gestational age at sampling (weeks)	9.4 (1.6)	9.6 (1.5)	0.620
Body mass index (kg/m ²)	28.3 (3.9)	24.9 (3.6)	0.004
Gravidity	2 (1-4)	2 (1-5)	0.710
Parity	1 (0-3)	1 (0-3)	0.830
Smoking status, n (%)	6 (20.0%)	10 (16.7%)	0.690

Data are presented as mean (standard deviation) or median (range), as appropriate. Group comparisons were performed using Student's t-test or the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Abbreviations: BMI: body mass index, SD: standard deviation. * $P < 0.05$ was considered statistically significant.

Serum kisspeptin-10 levels were significantly lower in pregnancies that resulted in spontaneous abortion than in ongoing pregnancies ($P = 0.001$) (Table 2).

In univariate logistic regression analysis, higher body mass index and lower serum kisspeptin-10 levels were identified as significant predictors of spontaneous abortion (Table 3). In the multivariate model, both variables remained independently associated with spontaneous abortion (Table 4).

Table 2. Serum Kisspeptin-10 Levels According to Pregnancy Outcome

Parameter	Spontaneous Abortion (n = 30)	Control Group (n = 60)	P-value
Serum kisspeptin-10 (ng/mL)	0.73 (0.67)	1.92 (2.78)	0.001

Serum kisspeptin-10 concentrations were measured between 7 and 12 weeks of gestation using an enzyme-linked immunosorbent assay. Comparisons were performed using the Mann-Whitney U test. * $P < 0.05$ was considered statistically significant.

Table 3. Univariate Logistic Regression Analysis for Predictors of Spontaneous Abortion

Variable	OR	95% CI	P-value
Maternal age (per year)	1.03	0.95-1.11	0.460
Gestational age (per week)	0.92	0.74-1.14	0.440
Body mass index (per kg/m ²)	1.18	1.05-1.33	0.004
Serum kisspeptin-10 (per ng/mL)	0.54	0.31-0.94	0.030

Univariate logistic regression analysis was performed to evaluate potential predictors of spontaneous abortion. Abbreviations: OR: odds ratio, CI: confidence interval. * $P < 0.05$ was considered statistically significant.

Table 4. Multivariate Logistic Regression Analysis of Independent Predictors of Spontaneous Abortion

Variable	Adjusted OR	95% CI	P-value
Body mass index (per kg/m ²)	1.21	1.06-1.38	0.004
Serum kisspeptin-10 (per ng/mL)	0.57	0.33-0.98	0.030

Multivariate logistic regression analysis adjusted for maternal age and gestational age at blood sampling. Abbreviations: OR: odds ratio, CI: confidence interval. * $P < 0.05$ was considered statistically significant.

Discussion

The present study demonstrates that reduced first-trimester serum kisspeptin-10 levels are associated with subsequent spontaneous abortion in pregnancies with confirmed fetal cardiac activity. By focusing specifically on clinically viable pregnancies, these findings provide evidence that biomarkers reflecting placental function may offer additional prognostic value beyond conventional embryonic markers.

Early pregnancy maintenance depends on tightly regulated trophoblastic invasion and placental development. Kisspeptins, primarily produced by placental trophoblasts, are known to modulate these processes through autocrine and

paracrine signaling pathways [14]. While β -hCG and progesterone measurements have limited predictive value after fetal cardiac activity is established, placental biomarkers such as kisspeptin offer a biologically plausible alternative [15].

The placenta represents the principal source of circulating kisspeptins during pregnancy [12, 16, 17]. Experimental studies have shown that kisspeptin signaling limits excessive trophoblast invasion while supporting angiogenesis and implantation. Therefore, reduced circulating kisspeptin levels may reflect impaired placentation and instability at the maternal-fetal interface, which are key mechanisms underlying early pregnancy loss. Previous clinical studies have consistently reported lower circulating kisspeptin levels in women with threatened miscarriage or early pregnancy loss [12, 18-20]. However, many of these studies included heterogeneous populations without confirmed fetal cardiac activity, limiting their clinical applicability. By restricting the study population to pregnancies with documented fetal viability, the present study addresses a more specific and clinically relevant scenario in which traditional biomarkers such as β -hCG and progesterone are less informative. In this context, kisspeptin may serve as a surrogate marker of placental integrity rather than embryonic development.

An additional important finding of this study is the independent association between increased maternal body mass index and spontaneous abortion. Maternal adiposity is associated with chronic low-grade inflammation, altered adipokine secretion, and metabolic dysregulation, all of which may adversely affect placental development and function. These pathways may influence trophoblastic activity and potentially modulate placental peptide secretion, including kisspeptin. This interaction suggests a biologically plausible link between obesity and impaired placental signaling, further contributing to pregnancy loss risk [21].

The findings of this study support the concept that placental biomarkers can enhance early pregnancy risk stratification. Unlike traditional markers that primarily reflect embryonic viability, kisspeptin appears to provide insight into placental function, which plays a central role in pregnancy maintenance. Integration of such biomarkers into clinical assessment may improve individualized counseling and monitoring strategies in early pregnancy.

Several limitations should be considered. The number of spontaneous abortion cases was relatively limited, and serum kisspeptin-10 levels were assessed at a single time point. Longitudinal measurements could provide a more comprehensive understanding of dynamic changes in placental function. In addition, correlation with placental histopathology was not available. Future studies with larger cohorts and serial measurements are needed to establish clinically applicable thresholds and to further elucidate the mechanistic role of kisspeptin in early pregnancy.

Conclusion

Lower first-trimester serum kisspeptin-10 levels were associated with an increased risk of spontaneous abortion in pregnancies with confirmed fetal cardiac activity. Serum kisspeptin-10 may serve as a supplementary biomarker for early pregnancy risk stratification; however, larger prospective studies

are needed to establish clinically applicable thresholds and validate its predictive performance.

References

- Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. *BMJ*. 2019;364:l869. <https://doi.org/10.1136/bmj.l869>
- George JS, Mortimer R, Anchan RM. Clinical updates in the management of recurrent pregnancy loss (RPL). *Curr Obstet Gynecol Rep*. 2022;11(2):118-24. <https://doi.org/10.1007/s13669-022-00328-5>
- Turesheva A, Aimagambetova G, Ukybassova T, Marat A, Kanabekova P, Kaldygulova L, et al. Recurrent pregnancy loss etiology, risk factors, diagnosis, and management. Fresh look into a full box. *J Clin Med*. 2023;12(12):4074. <https://doi.org/10.3390/jcm12124074>
- Petersen JF, Friis-Hansen LJ, Bryndorf T, Jensen AK, Andersen AN, Løkkegaard E. A novel approach to predicting early pregnancy outcomes dynamically in a prospective cohort using repeated ultrasound and serum biomarkers. *Reprod Sci*. 2023;30(12):3597-609. <https://doi.org/10.1007/s43032-023-01323-8>
- Tsutsui K, Ubuka T. Photoperiodism in mammalian reproduction. In: Skinner MK, editor. *Encyclopedia of Reproduction*. 2nd ed. Vol. 6. Oxford: Academic Press; 2018. p. 415-9. <https://doi.org/10.1016/B978-0-12-809633-8.20586-4>
- Xie Q, Kang Y, Zhang C, Xie Y, Wang C, Liu J, et al. The role of kisspeptin in the control of the hypothalamic-pituitary-gonadal axis and reproduction. *Front Endocrinol (Lausanne)*. 2022;13:925206. <https://doi.org/10.3389/fendo.2022.925206>
- Oakley AE, Clifton DK, Steiner RA. Kisspeptin signaling in the brain. *Endocr Rev*. 2009;30(6):713-43. <https://doi.org/10.1210/er.2009-0005>
- Gomes VCL, Sones JL. From inhibition of trophoblast cell invasion to proapoptosis: what are the potential roles of kisspeptins in preeclampsia? *Am J Physiol Regul Integr Comp Physiol*. 2021;321(1):R41-8. <https://doi.org/10.1152/ajpregu.00258.2020>
- Hidden U, Bilban M, Knöfler M, Desoye G. Kisspeptins and the placenta: regulation of trophoblast invasion. *Rev Endocr Metab Disord*. 2007;8(1):31-9. <https://doi.org/10.1007/s11154-007-9030-8>
- Francis VA, Abera AB, Matjila M, Millar RP, Katz AA. Kisspeptin regulation of genes involved in cell invasion and angiogenesis in first trimester human trophoblast cells. *PLoS One*. 2014;9(6):e99680. <https://doi.org/10.1371/journal.pone.0099680>
- Panting EN, Weight JH, Sartori JA, Coall DA, Smith JT. The role of placental kisspeptin in trophoblast invasion and migration: an assessment in Kiss1r knockout mice, BeWo cell lines and human term placenta. *Reprod Fertil Dev*. 2024;36(11):RD23230. <https://doi.org/10.1071/RD23230>
- Ye S, Zhou L. Role of serum kisspeptin as a biomarker to detect miscarriage: a systematic review and meta-analysis. *Hum Fertil (Camb)*. 2024;27(1):2417934. <https://doi.org/10.1080/14647273.2024.2417934>
- Liu L, Lin Z, Lai X, Wu S. Circulating kisspeptin levels in spontaneous abortion: a systematic review and meta-analysis. *Clin Exp Obstet Gynecol*. 2023;50(5):101. <https://doi.org/10.31083/j.ceog5005101>
- Jauniaux E, Burton GJ. Pathophysiology of histological changes in early pregnancy loss. *Placenta*. 2005;26(2-3):114-23. <https://doi.org/10.1016/j.placenta.2004.05.011>
- Memtsa M, Jurkovic D, Jauniaux ERM, Royal College of Obstetricians and Gynaecologists. Diagnostic biomarkers for predicting adverse early pregnancy outcomes. *BJOG*. 2019;126(3):e107-13. <https://doi.org/10.1111/1471-0528.15468>
- Musa E, Matjila M, Levitt NS. Kisspeptins and glucose homeostasis in pregnancy: implications for gestational diabetes mellitus-a review article. *Reprod Sci*. 2022;29(2):321-7. <https://doi.org/10.1007/s43032-020-00437-7>
- Bowe JE, Hill TG, Hunt KF, Smith LIF, Simpson SJS, Amiel SA, et al. A role for placental kisspeptin in β cell adaptation to pregnancy. *JCI Insight*. 2019;4(20):e124540. <https://doi.org/10.1172/jci.insight.124540>
- da Silva PHA, de Melo Romão LG, de Freitas NPA, Carvalho TR, Porto MEMP, Araujo Júnior E, et al. Kisspeptin as a predictor of miscarriage: a systematic review. *J Matern Fetal Neonatal Med*. 2023;36(1):2197097. <https://doi.org/10.1080/14767058.2023.2197097>
- Li H, Zhang W, Sun X. A prospective study to evaluate whether serum kisspeptin is a marker predictive of the first-trimester miscarriage of women who conceive in IVF. *J Assist Reprod Genet*. 2024;41(1):79-85. <https://doi.org/10.1007/s10815-023-02974-x>
- Abbara A, Al-Memar M, Phylactou M, Daniels E, Patel B, Eng PC, et al. Changes in circulating kisspeptin levels during each trimester in women with antenatal complications. *J Clin Endocrinol Metab*. 2022;107(1):e71-83. <https://doi.org/10.1210/clinem/dgab617>
- Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril*. 2008;90(3):714-26. <https://doi.org/10.1016/j.fertnstert.2007.07.1290>

Disclaimer/Publisher's Note: The statements, opinions, and data presented in publications in the Journal of Surgery and Medicine (JOSAM) are exclusively those of the individual author(s) and contributor(s) and do not necessarily reflect the views of JOSAM, the publisher, or the editor(s). JOSAM, the publisher, and the editor(s) disclaim any liability for any harm to individuals or damage to property that may arise from implementing any ideas, methods, instructions, or products referenced within the content. Authors are responsible for all content in their article(s), including the accuracy of facts, statements, and citations. Authors are responsible for obtaining permission from the previous publisher or copyright holder if re-using any part of a paper (e.g., figures) published elsewhere. The publisher, editors, and their respective employees are not responsible or liable for the use of any potentially inaccurate or misleading data, opinions, or information contained within the articles on the journal's website.